07/27/04

1624

CASE 4-30972A

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
BRAIN ET AL.
APPLICATION NO: 10/009,009
FILED: DECEMBER 20, 2001
FOR: BRADYKININ RECEPTOR ANTAGONISTS

Art Unit: 1624
Examiner: T. McKenzie

Attention: Janet Higgins
U.S. Patent and Trademark Office
2231 Crystal Drive
Suite 910
Arlington, VA 22202

COMMUNICATION

Sir:

As per our discussion by telephone today to supply you with legible copies of pages 10 and 11 of this application, enclosed are replacement pages 10 and 11 for your records.

Please do not hesitate to call if you have further questions.

Respectfully submitted,

Edward J. Wilusz, Jr.
Attorney for Applicants
Reg. No. 52,370
(862) 778-7960

Novartis
Corporate Intellectual Property
One Health Plaza, Building 430
East Hanover, NJ 07936-1080

Date: July 26, 2004

Compound	R^{3A}	m	n	R^{6A}
5.23	5-methylisoxazol-3-ylmethyl	2	0	$-CH_3$
5.24	2-methylthiazol-4-ylmethyl	2	0	$-CH_3$
5.25	$-CH_2CHC(CH_3)_2$	2	0	$-CH_3$
5.26	$-CH_2CHCHCH_3$	2	0	$-CH_3$
5.27	$-CH_2C_6H_{11}$	2	0	$-CH_3$
5.28	$-CH_2C_4H_7$	2	0	$-CH_3$
5.29	$-CH_2CCCH_3$	2	0	$-CH_3$
5.30	thiophen-3-ylmethyl	2	0	$-CH_3$
5.31	thiophen-2-ylmethyl	2	0	$-CH_3$
5.32	$-CH_2CCCH_2CH_3$	2	0	$-CH_3$
5.33	$-CH(CH_3)_2$	2	0	$-CH_3$

CHARACTERISING DATA

Compounds of the above tables are found to exhibit the following HPLC retention data [min]:

No.	[min]	No.	[min]	No.	[min]	No.	[min]
1	5.91*	1.5	7.17****	26	24.95***	5.15	6.083*
2	5.68*	1.6	5.0*****	27	5.90*	5.16	6.100*
3	6.22*	1.7	5.7*****	28	6.23*	5.17	6.067*
4	5.43**	16	24.03***	29	5.35*	5.18	5.967*
5	23.55***	17	4.6****	30	5.75*	5.19	4.767*
6	5.24**	18	20.1***	5.1	5.833*	5.20	4.667*
7	25.93***	19	22.6***	5.2	6.367*	5.21	5.567*
8	5.09**	20	22.58***	5.3	6.100*	5.22	6.02*
9	23.98***	21	27.57***	5.4	6.250*	5.23	6.138*
10	23.89***	22	22.9***	5.5	6.167*	5.24	6.087*
11	6.37*	3.1	5.03*****	5.6	6.45*	5.25	6.558*
12	23.68***	3.2	5.8*	5.7	6.200*	5.26	6.382*
13	5.10**	3.3	5.83*	5.8	5.467	5.27	6.932*
14	6.17****	3.4	3.4*****	5.9	6.167*	5.28	6.547*
15	5.28****	4.1	5.467*	5.10	5.900*	5.29	6.26*
1.1	4.95*****	4.2	5.822*	5.11	6.338*	5.30	6.453*

No.	[min]	No.	[min]	No.	[min]	No.	[min]
1.2	6.00****	23	5.57*	5.12	6.998*	5.31	5.7*****
1.3	6.4****	24	5.9*	5.13	6.983*	5.32	5.7*****
1.4	6.82****	25	23.82***	5.14	7.03*	5.33	6.510*

HPLC conditions:

*: Hypersil 3 micron C 18 BDS column. Gradient elution 10-100% MeCN in water (+0.1% TFA) over 10 min

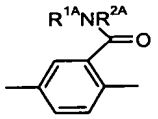
**: Kingsorb 50x4.6mm C18 column, 3micron particle size; flow rate 3ml/min; 90% water (+10mM NH_4OAc 0.3% HCOOH) 10% MeCN to 100% MeCN over 10min

***: Nucleosil 5 micron C18 column, 25cm x 4.6mm. Gradient elution 10-100% MeCN in water (+0.1% TFA) over 40 min

****: Waters Symmetry 3 micron C18 column; 5 x 0.46 cm. Gradient elution, 10% to 100% MeCN in water (+ 0.1% TFA) over 10 min

*****: Kingsorb 3 micron C18 column, 30x4.6mm, gradient elution 10 % MeCN in water (+0.1% TFA) to 100% MeCN over 10 min

Compounds of formula IIA wherein X^1, R^9 and R^{10} have the above meanings and X^2 is a divalent group of formula



wherein R^{1A} and R^{2A} independently are C_1-C_4alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring,

may be prepared applying known techniques, e.g. in accordance with the following reaction scheme: